UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,006	08/24/2000	Patrick Tso	10738-17	5310

7590 04/06/2006

Dinsmore & Shohl
1900 Chemed Center
255 East Fifth Street
Cincinnati, OH 45202

EXAMINER	
MITRA, RITA	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,006	TSO ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-14,19 and 64-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4,-14, 19, 64-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Applicants' amendment and response to office action dated September 8, 2005, filed on December 12, 2005, is acknowledged. Claims 2, 3, 15-18 and 20-63 have been canceled. New claims 65 and 66 have been added. Therefore, claims 1, 4-14, 19 and 64-66 are currently under examination.

Response to Remarks and Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-14, 19 and 64-66 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4, 13, 14, 19 and 64-66 encompass the subject matter that is not defined in the specification. The claims are drawn to a method for inhibiting lipid oxidation associated with a condition in a patient, comprising administering to a patient a composition comprising a pharmacologically effective amount of an apolipoprotein (apo) A-IV peptide, to inhibit lipid oxidation. Additionally the claimed invention asserts that the apolipoprotein A-IV is a peptide sequence of from 6-71 amino acids in length and wherein the peptide has substantially the same lipid oxidation properties as the apolipoprotein A-IV molecule. The specification, (see page 6, lines 3-6), states that a number of novel lipid oxidation suppressant peptides, derived from apolipoprotein A-I, have been made, these peptides possess lipid oxidation inhibiting properties which when administered orally or intravenously, can be used to decrease atherosclerosis.

However, the specification does not describe the specific structure and function of these sequence fragments of apolipoprotein A-IV. The apolipoprotein A-IV peptide sequences of from 6-71 amino acids would encompass several variants of amino acids in length starting from 6, 7, 8, 9.....up to 71 amino acids. Moreover, 6-71 amino acids in length neither gives a clear definition, whether the sequence is derived from a native apolipoprotein A-IV, nor a sequence identifier has been given to this sequence. As it is stated at page 12 that the invention provides for a number of lipid oxidation inhibiting peptides of approximately 5-90 amino acids in length, which substantially correspond in sequence to amino acid sequence found in specific portions of apo AIV, which is insufficient description as no characteristics are provided nor any evidence to demonstrate retention of function with regard to inhibitory activity in lipid oxidation. Moreover based on open language "comprising", the claimed apolipoprotein can have sequences added to the N-terminal or C-terminal end and any polypeptide or peptide, having an undefined structure.

Claim 4 is drawn to the method of claim 1, wherein the peptide has an amino acid sequence comprising amino acid sequence set forth in SEQ ID NO: 5. However, the specification provides only a generic description of how a variety of variants or fragments can be generated (page 22-26), no specific guidance is provided on the generation of the variants or fragment that demonstrate the biological activity of the peptide sequence of SEQ ID NO: 5. However the specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the apolipoprotein AIV, which comprises variants and fragments, which have substantially the same lipid oxidation properties as the apolipoprotein AIV wild-type molecule. Furthermore, there is no written description of either a representative number of the variants or of a common structural feature of the native apo AIV that encompasses all the variants.

The rejection is set forth in prior office action. In response Applicants traverse the rejection (see page 7). The reason for the traversal is the apolipoprotein A-IV peptide is from 6-71 amino acids in length and the peptide has substantially the same lipid oxidation properties as the apolipoprotein A-IV molecule. Applicants' arguments have been fully considered but not found persuasive because the specification does not provide a description of "6-71" amino acids, that includes specific structure and function of these fragments (see discussion supra). As it is

stated at page 12 that the invention provides for a number of lipid oxidation inhibiting peptides of approximately 5-90 amino acids in length, which substantially correspond in sequence to amino acid sequence found in specific portions of apo A-IV, which is insufficient description because it does not describe that portion of apo A-IV, to which amino acids sequence of the claimed peptides correspond. The sequence of that portion cannot be correlated to any claimed peptide sequence as no characteristics are provided nor any evidence to demonstrate retention of function with regard to inhibitory activity in lipid oxidation.

Applicants assert at page 8 that over a dozen representative peptides are disclosed in detail on pages 7-8 of the specification. However, the specification fails to describe any property, which would demonstrate retention of function with regard to inhibitory activity in lipid oxidation. At page 10 Applicants indicate that they have disclosed experiments with results that fully support this. In response Applicants' attention is drawn to the disclosed Examples (pages 39-43), where only full length Apo A-IV have been used not their fragments or variants including SEQ ID NO: 5 (claim 4).

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding the active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitution or no substitutions. However, the specification provides no description of the positions in the protein, which are tolerant to change (e.g. by amino acid substitutions or deletions, insertion or/and addition), and the nature and extent of changes that can be made in these positions. Therefore, the skilled artisan cannot envision the detailed chemical structure of the apolipoprotein variants and fragments, thus, claims reciting said variants and/or fragments lack adequate written description.

Claim rejection - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-14, 19 and 64-66 stand/are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting lipid oxidation associated with a condition in a patient comprising administering an apolipoprotein A-IV compound does not reasonably provide enablement for a method for inhibiting lipid oxidation comprising administering all apolipoprotein A-IV variants/fragments. The specification does not enable persons skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4-14,19 and 64-66 encompass a method for inhibiting lipid oxidation associated with a condition in a patient comprising administering a composition comprising apolipoprotein A-IV compound, wherein the compound is a peptide sequence (claims 1, 4-14, 19, 64-66), wherein said peptide is from 6-71 amino acids in length; wherein the peptide has an amino acid sequence comprising the sequence of SEQ ID NO: 5 (claim 4).

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands 858 F.2d 731, 8 USPQ2d 1404 (Fed. Cir, 1988)*. The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

In the instant case, the amount of experimentation is required to practice the claimed invention is undue as the claims encompass an unspecified amount of apolipoprotein A-IV peptides and variants/fragments of sequences of from 6-71 amino acids in length. One of skill in

the art would have to make and test each one to determine if it had the apo A-IV activity of the parent protein. The amount of guidance presented is limited to the exact sequence.

There are no indicia that the present application enables the full scope in view of treating conditions associated with lipid oxidation comprising administering an apolipoprotein A-IV variant as discussed in the following stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled.

The claims are drawn to a method of lipid oxidation associated with a condition in a patient comprising administering an apolipoprotein A-IV compound, wherein the compound is a peptide sequence, and a fragment of apolipoprotein A-IV. However, the specification only indicates apolipoprotein A-IV protein effective in protection against lipid oxidation (Examples, page 39-43, Fig 1-4), there is no disclosure or description of the use of other apo A-IV protein fragments. There are no working examples indicating the claimed methods in association with the variants. Moreover, the specification has not shown the treating conditions using these apo A-IV variants. Furthermore, the specification does not provide any specific guidance on treating conditions such as the patient population, dosage, regimen, routes of administration, the time and the treatment schedule as well as the effect of the apo A-IV variants, nor indicated the expected outcome of treatment. Since the specification fails to provide sufficient guidance on the treating conditions for various apo A-IV variants, it is necessary to have additional guidance on the identities of apo A-IV variants and to carry out further experimentation to assess the effect of an apo A-IV variant, which is used for the treatment. Without more guidance from the specification it would require undue and excessive experimentation for a person having skill in the art to be able to make and use the claimed variants.

The scope of the claims includes method of lipid oxidation associated with a condition in a patient comprising administering an apolipoprotein A-IV compound, wherein the compound is a peptide sequence, and a variant or fragment of apolipoprotein A-IV, but the specification does not show the treatment using these variants. The nature of the variants makes it entirely unpredictable what might be considered a variant before the isolation of such a sequence has actually taken place Thus, the disclosure is not enabling for the reasons discussed below.

The prior art has shown that apolipoprotein A-IV protein, is effective as endogenous

inhibitor of lipid oxidation (see Boguski et al. 1984), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the treating conditions such as the dosage, the time and the effect for treating conditions associated with lipid oxidation for various apo A-IV protein products to be considered enabling for variants.

The breadth of the claims is broad and encompasses an unspecified number of variants regarding the apolipoprotein A-IV protein products as biological active fragments, which are not specifically described or demonstrated in the specification. The specification indicates at page 6, lines 3-6 that a number of novel lipid oxidation suppressant peptides, derived from apolipoprotein A-IV, have been made, that possess lipid oxidation inhibiting properties which when administered orally or intravenously, can be used to decrease atherosclerosis. However, these peptides are not adequately described or demonstrated in the specification.

Claim 4 requires a functional fragment of a peptide sequence of apolipoprotein A-IV compound, therefore at least includes the amino acid sequence that has lipid oxidation inhibition activity. However, the disclosure fails to provide a description of a variant that demonstrates such activity. Therefore, as the specification fails to describe adequately the structure and function of those apolipoprotein variants, one skilled in the art would not recognize a specific utility for the variants and would not know how to use them. Thus, for the reasons set forth above, undue experimentation is required to make and use the claimed apolipoprotein variants. Although the specification outlines art-recognized procedures for producing variants and fragments (pages 14, 15, 21-23), this is not adequate guidance as to the nature of functional derivatives that may be constructed. Thus, further experimentation is required to make and use the claimed invention.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable using various apolipoprotein A-IV products, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the treatment using a apolipoprotein A-IV variants.

The rejection is set forth in prior office action. In response Applicants traverse the rejection (see page 10-15). The reason for the traversal in particular is with respect to working

examples. It should be noted that there are no working examples indicating the claimed methods in association with the variants. Moreover, the specification has not shown the treating conditions using these apo A-IV variants. The requirement of a specific guidance on treating conditions, does not necessarily require disclosures of clinical data as interpreted and stated by the Applicants at page 13. The specification and the working examples do not provide any guidance with respect to use of the fragments or variants for the treatment. Since the specification fails to provide sufficient guidance on the treating conditions for various apo A-IV variants, it is necessary to have additional guidance on the identities of apo A-IV variants and to carry out further experimentation to assess the effect of an apo A-IV variant, which is used for the treatment.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however; will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita Mitra whose telephone number is 571-272-0954. The examiner can normally be reached on M-F, 10:00 am-7:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rita Mitra, Ph.D.
March 30, 2006

JON WEBER
SUPERVISORY PATENT EXAMINER